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Prospective Study of Diet, Lifestyle, and Intermittent Claudication in Male Smokers

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The association between dietary and lifestyle factors and intermittent claudication was investigated in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. The cohort comprised 26,872 male smokers aged 50–69 years who were free of claudication at study entry. At baseline (1985–1988), subjects completed a diet history questionnaire. During a median follow-up period of 4 years (ending in spring 1993), 2,578 men reported symptoms of claudication on the Rose questionnaire, which was administered annually. Smoking status was assessed every 4 months. Smoking, systolic blood pressure, serum total cholesterol, and diabetes mellitus were positively associated with risk for claudication, whereas serum high density lipoprotein cholesterol, education, and leisure time exercise were inversely associated with risk. Dietary carbohydrates, fiber, and n-6 polyunsaturated fatty acids were inversely associated with risk for claudication, as were some dietary and serum antioxidants: dietary vitamin C (highest quartile vs. lowest: relative risk (RR) = 0.86; 95% confidence interval (CI): 0.77, 0.97), dietary γ-tocopherol (RR = 0.89; 95% CI: 0.79, 1.00), dietary carotenoids (RR = 0.82; 95% CI: 0.73, 0.92), serum α-tocopherol (RR = 0.88; 95% CI: 0.77, 1.00), and serum β-carotene (RR = 0.77; 95% CI: 0.68, 0.86). Smoking cessation reduced subsequent risk for claudication (RR = 0.86; 95% CI: 0.75, 0.99). The authors conclude that classical risk factors for atherosclerosis are associated with claudication. High intakes of antioxidant vitamins may be protective. Further research is needed before antioxidants can be recommended for the prevention of intermittent claudication. *Am J Epidemiol* 2000; 151:892–901.

antioxidants; cohort studies; diet; intermittent claudication; smoking

Atherosclerosis in the arteries of the lower extremities can result in insufficient blood flow during exercise, leading to intermittent claudication. Intermittent claudication is a common disorder among older people, limiting their everyday activities. It is also associated with increased risk for cardiovascular disease mortality (1, 2). Although intermittent claudication is a well known disorder, its determinants have not been investigated as thoroughly as have those of coronary heart disease. Several case-control and cohort studies have revealed smoking to be the most important risk factor for intermittent claudication (3–9). Other reported risk factors are diabetes mellitus, elevated serum cholesterol levels, and elevated blood pressure.

Diet is linked to atherosclerosis. The Seven Countries Study showed that populations with a high intake of saturated fat and a low intake of monounsaturated fat had higher cardiovascular disease mortality (10), but within cohorts dietary fats have shown a weak association with coronary heart disease or none at all (11–13). In several prospective studies, inverse associations were found to exist between dietary and supplemental intakes of antioxidant vitamins and risk for coronary heart disease or cardiovascular disease mortality (14–18). However, data on the role of these nutrients in the etiology of peripheral arterial occlusive disease are limited. High intakes of fiber, vitamins E and C, polyunsaturated fatty acids, and alcohol were associated with higher ankle-brachial blood pressure index in a cross-sectional study (19) and with lower risk for peripheral arterial occlusive disease in a case-control study (20). High intakes of saturated fatty acids, protein, and dietary cholesterol have been associated with increased risk for peripheral arterial occlusive disease (20).

The effect of α-tocopherol and β-carotene supplementation on primary prevention of intermittent claudication has been evaluated in the Finnish Alpha-

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Abbreviations: ATBC Study, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; HDL, high density lipoprotein; RR, relative risk.

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Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (21). The aim of this study was to examine the association of well known atherosclerotic risk factors with intermittent claudication and to assess the effect of smoking cessation on claudication incidence in the trial cohort of the ATBC Study. We also investigated associations between several dietary nutrients and serum α-tocopherol and β-carotene levels and risk for intermittent claudication.

MATERIALS AND METHODS

The subjects of this study were participants in the ATBC Study, a randomized, double-blind, placebo-controlled trial primarily aimed at examining the effect of antioxidant supplementation on cancer (22). Participants were recruited from the total male population aged 50–69 years living in southwestern Finland (n = 290,406). Enrollment took place from 1985 through 1988, and the study lasted until spring 1993. To be eligible, participants had to smoke at least five cigarettes per day at study entry. Exclusion criteria were previous cancer, any serious disease limiting long term participation, and current use of anticoagulants, vitamin E, β-carotene, or vitamin A supplements (however, ≤20 mg of α-tocopherol, ≤6 mg of β-carotene, and ≤20,000 IU of vitamin A per day were permitted). A total of 29,133 men were randomly assigned in blocks of eight to four supplementation groups: 50 mg of α-tocopherol (DL-α-tocopheryl acetate), 20 mg of β-carotene, both, or placebo, each in one daily capsule. All participants gave written informed consent before randomization. The ATBC Study was approved by the institutional review boards of the Finnish National Public Health Institute (Helsinki, Finland) and the US National Cancer Institute (Bethesda, Maryland).

At baseline, 2,261 men reported a history of intermittent claudication or symptoms of typical intermittent claudication on the Rose questionnaire (23) and were excluded, leaving 26,872 men in this cohort. Data on smoking habits, medical history, education, and leisure time physical activity were collected through questionnaires administered at baseline. Weight, height, and blood pressure were recorded. A blood sample was drawn, and serum was stored at –70°C. Levels of serum total cholesterol and high density lipoprotein (HDL) cholesterol were determined enzymatically using the CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany; kit no. 124966) (24). HDL cholesterol was measured after precipitation with dextran sulfate and magnesium chloride (25). Serum α-tocopherol and β-carotene concentrations were measured by high performance liquid chromatography (26).

Usual diet, including alcohol consumption over the previous 12 months, was assessed with a self-administered diet history questionnaire. The questionnaire was satisfactorily completed by 25,023 (93 percent) men. This questionnaire covered the consumption of approximately 200 food items and 70 mixed dishes. A picture booklet with color photographs of foods, each with 3–5 different portion sizes, served to specify usual consumption. The reproducibility and validity of this questionnaire were found to be satisfactory in a pilot study carried out among 190 men prior to the ATBC Study (27). Food consumption and nutrient intakes were computed using the database of the National Public Health Institute.

During follow-up, participants visited their local study centers three times per year, and they were asked about current smoking at each visit. If a subject had not smoked during two consecutive 4-month follow-up periods, he was defined as having stopped smoking. Once per year, study nurses reinterviewed participants about any intermittent claudication, using the Rose questionnaire. The first occurrence of typical symptoms was recorded as the endpoint (n = 2,578), with typical intermittent claudication being defined as pain in one or both calves induced upon exertion and relieved by a rest of no longer than 10 minutes. The follow-up time of this study (median 4.0 years) lasted until the first occurrence of intermittent claudication or the last follow-up visit during which the Rose questionnaire was administered. Thirty percent of the participants without previous intermittent claudication dropped out of the study before their final scheduled annual administration of the Rose questionnaire.

Statistics

Several risk factors for intermittent claudication were under study: age, systolic and diastolic blood pressure, serum total and HDL cholesterol, body mass index (weight (kg)/height $(m)^2$), years of smoking, number of cigarettes smoked daily (all categorized), leisure time exercise (no exercise vs. slight to moderate exercise), history of diabetes, and education (elementary school vs. junior high school or more). The effect of these factors on risk for intermittent claudication was analyzed by the Cox proportional hazards model with simultaneous adjustment for all of these factors and α-tocopherol and β-carotene supplementation as the main effects, without their interaction (α-tocopherol supplementation vs. no α-tocopherol supplementation and β-carotene supplementation vs. no β-carotene supplementation). Significance was tested by means of the likelihood ratio test. Because diastolic blood pressure and body mass index were not independently associated with risk for claudication and did not significantly modify the effect of other risk factors

on intermittent claudication, they were not included in the following multivariate models. Cessation of smoking was used as a time-dependent variable and analyzed by the Cox proportional hazards model with simultaneous adjustment for the other risk factors.

Data on all nutrient intakes except alcohol intake were log-transformed and energy-corrected by the residual method (28) and divided into quartiles, with the lowest quartile designated the reference group. Cox models were used to estimate relative risks for intermittent claudication associated with energy-adjusted intakes of the nutrients, with simultaneous adjustment for age, smoking habits (number of cigarettes smoked per day and years of smoking), and intake of energy. Each nutrient was added to the model separately. In further analyses, the other risk factors (systolic blood pressure, total and HDL cholesterol, leisure time exercise, history of diabetes, education, α-tocopherol and β-carotene supplementation, and smoking cessation) were included in the model. The linearity of the trend was tested by means of the Wald test, where an ordinal variable with quartile scores was refitted and a coefficient of it was tested. Interaction between smoking habits (years of smoking and daily number of cigarettes smoked) and intake of antioxidant vitamins was tested by means of the likelihood ratio test. In the analyses of nutrients, we had 2,407 incident cases of claudication.

In addition, associations between baseline serum α-tocopherol and β-carotene concentrations and risk for intermittent claudication were assessed using Cox models. First, serum levels were adjusted for age, smoking habits, and total and HDL cholesterol levels; second, a multivariate model was created including the other risk factors. The linearity of the trend was tested by means of the Wald test.

RESULTS

The mean age of the subjects was 58 years. They had smoked, on average, for 36 years, and at entry they smoked a mean of 20 cigarettes per day. Their mean systolic blood pressure was 142 mmHg, and their mean diastolic pressure was 88 mmHg. The mean serum total cholesterol level was 6.22 mmol/liter, and the mean HDL cholesterol level was 1.18 mmol/liter. A basic education of only elementary school was reported by 84 percent of the men. Four percent reported a history of diabetes, and 59 percent engaged in at least light exercise during their leisure time. In the multivariate model, risk for intermittent claudication was significantly higher with increasing age, number of cigarettes smoked per day, years of smoking, systolic blood pressure, and serum total cholesterol level and with a history of diabetes. Higher levels of HDL cholesterol and leisure time exercise and basic education were associated with lower risk (figure 1).

We also assessed the effect of smoking cessation on risk for developing claudication. During follow-up, 4,538 (17 percent) subjects stopped smoking. Of these men, 271 reported subsequent claudication during a follow-up period of 2.4 years. In a multivariate model, smoking cessation significantly reduced risk for claudication; the subsequent relative risk was 0.86 (95 percent confidence interval (CI): 0.75, 0.99).

Mean total energy intake was 2,826 kcal/day. Intake of energy was inversely associated with risk for intermittent claudication (highest quartile vs. lowest: relative risk (RR) = 0.79 (95 percent CI: 0.61, 1.02); p for linear trend = 0.03) (table 1). Of the macronutrients, high intakes of carbohydrates and fiber were significantly associated with decreased risk for intermittent claudication in both the age- and smoking-adjusted model and the multivariate model (highest quartile of carbohydrates vs. lowest: multivariate RR = 0.86 (95 percent CI: 0.76, 0.96); p for linear trend = 0.005; highest quartile of fiber vs. lowest: multivariate RR = 0.87 (95 percent CI: 0.77, 0.97); p for linear trend = 0.002). Intakes of fat and protein and alcohol consumption showed no association with risk for claudication (table 1). We found similar results when serum cholesterol or systolic blood pressure was omitted from the multivariate models.

Intake of polyunsaturated fatty acids showed a significant inverse association with intermittent claudication in the age- and smoking-adjusted model but not in the multivariate model (table 2). Eighty percent of polyunsaturated fatty acids consisted of n-6 fatty acids, and 20 percent consisted of n-3 fatty acids. Intake of n-6 polyunsaturated fatty acids was inversely associated with risk for claudication in both the age- and smoking-adjusted model and the multivariate model (highest quartile vs. lowest: multivariate RR = 0.91 (95 percent CI: 0.81, 1.02); p for linear trend = 0.048), whereas n-3 polyunsaturated fatty acids showed no association. However, the majority of n-3 polyunsaturated fatty acids were of vegetable origin, with only 20 percent being derived from fish. Neither dietary cholesterol, saturated fatty acids, nor *cis*- or *trans*-monounsaturated fatty acids showed any effect on risk for claudication (table 2). Similar associations were found when serum cholesterol or systolic blood pressure was not included in the multivariate model.

A higher intake of carotenoids (the sum of β-carotene, α-carotene, γ-carotene, lycopene, capsanthin, cryptoxanthin, canthaxanthin, lutein, and zeaxanthin intakes) was significantly associated with lower risk for claudication in both the age- and smoking-adjusted model and the multivariate model (highest

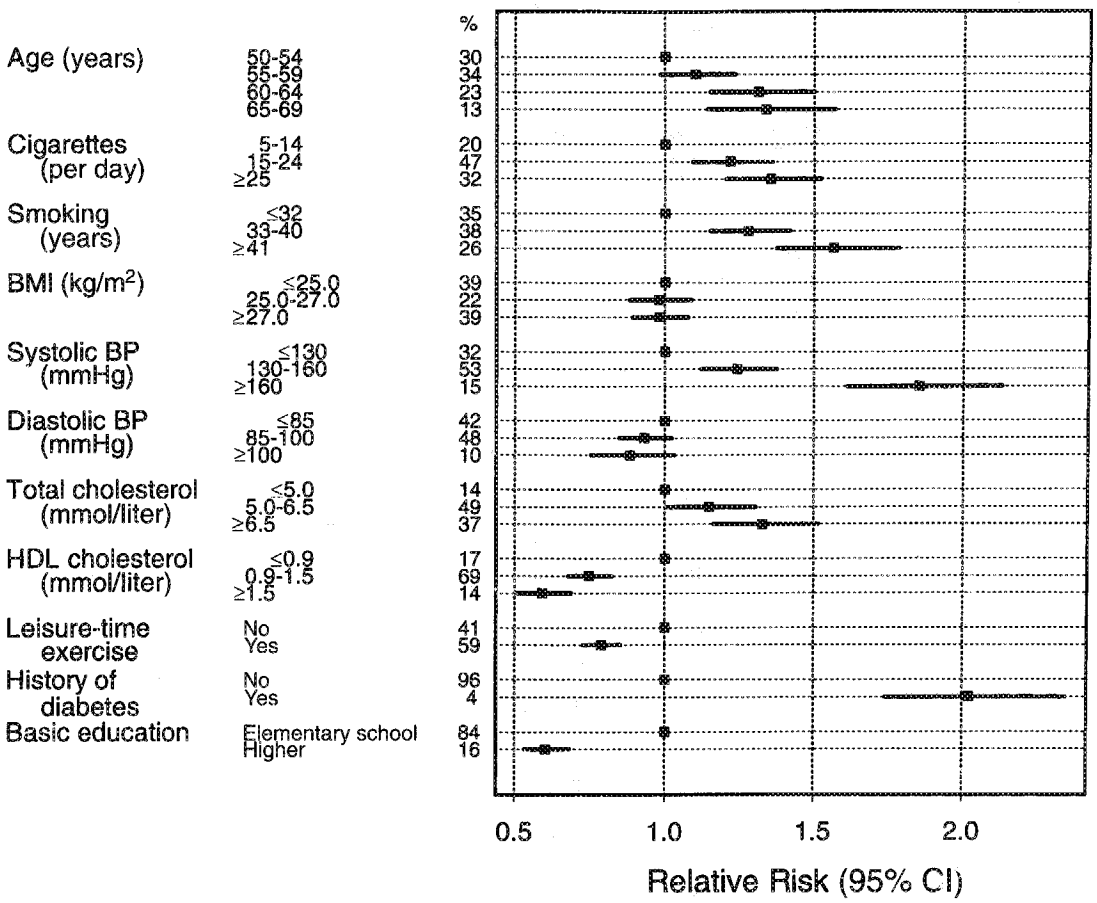

FIGURE 1. Relative risk (and 95% confidence interval (CI)) for intermittent claudication according to level of various factors, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–1993. Data were adjusted for baseline age, years of smoking, number of cigarettes smoked per day, serum total and high density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressure (BP), body mass index (BMI), basic education, leisure time exercise, history of diabetes, and α-tocopherol and β-carotene supplementation.

quartile vs. lowest: multivariate RR = 0.82 (95 percent CI: 0.73, 0.92); p for linear trend < 0.001) (table 3). Of the carotenoids, β-carotene, lycopene, and lutein + zeaxanthin showed a significantly lower risk for claudication with increasing levels of intake, whereas α-carotene was not associated with risk for claudication (table 3). Intakes of vitamin E and its main constituents, α-tocopherol and γ-tocopherol, were significantly inversely associated with risk for claudication in the age- and smoking-adjusted model, but after multivariate adjustment only γ-tocopherol retained a significant association (highest quartile vs. lowest: multivariate RR = 0.89 (95 percent CI: 0.79, 1.00); p for linear trend = 0.02) (table 3). Intake of vitamin C showed a significant inverse association with risk for claudication in both the age- and smoking-adjusted model and the multivariate model (highest quartile vs. lowest: multivariate RR = 0.86 (95 percent CI: 0.77, 0.97); p for linear trend = 0.004). Selenium intake was not associated with risk for claudication. Neither daily number of cigarettes smoked nor years of smoking modified the association between antioxidant intake and risk for claudication.

In further analysis, intakes of vitamin C and carotenoids were added to the multivariate model simultaneously. Intake of carotenoids retained its significant inverse association (highest quartile vs. lowest: RR = 0.84 (95 percent CI: 0.69, 0.95); p for linear trend = 0.008), but intake of vitamin C was no longer associated with risk for claudication. Similarly, we analyzed intakes of β-carotene, lycopene, and lutein + zeaxanthin simultaneously in a multivariate model and found that lycopene (highest quartile vs. lowest: RR = 0.87 (95 percent CI: 0.73, 0.99); p for linear trend = 0.03) and lutein + zeaxanthin (highest quartile vs. lowest: RR = 0.85 (95 percent CI: 0.70, 0.97); p for linear trend = 0.01) retained their protective effect, whereas β-carotene was not significantly associated with claudication risk.

The mean concentration of serum α-tocopherol was 11.9 mg/liter, and that of serum β-carotene 213

TABLE 1. Quartile cutpoints for daily intakes of energy and macronutrients and relative risks for intermittent claudication, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–1993*

Macronutrient	Quartile cutpoints	Age- and smoking-adjusted relative risk†	95% confidence interval	*p* for trend‡	Multivariate relative risk§	95% confidence interval	*p* for trend
Total energy (kcal)		1.00¶			1.00		
	2,269	0.87	0.78, 0.97		0.84	0.74, 0.96	
	2,733	0.92	0.82, 1.03		0.85	0.72, 1.01	
	3,271	0.91	0.81, 1.02	0.03	0.79	0.61, 1.02	0.03
Fat (g)		1.00			1.00		
	94	1.00	0.89, 1.13		1.00	0.89, 1.13	
	118	0.99	0.88, 1.11		0.98	0.87, 1.10	
	146	1.15	1.03, 1.28	0.17	1.12	1.00, 1.25	0.33
Protein (g)		1.00			1.00		
	83	1.03	0.92, 1.15		1.01	0.91, 1.14	
	111	1.03	0.92, 1.15		1.00	0.89, 1.12	
	120	1.10	0.98, 1.23	0.18	1.03	0.92, 1.16	0.73
Carbohydrates (g)		1.00			1.00		
	239	0.93	0.83, 1.04		0.93	0.83, 1.04	
	294	0.88	0.78, 0.98		0.87	0.78, 0.98	
	359	0.86	0.77, 0.97	0.006	0.86	0.76, 0.96	0.005
Fiber (g)		1.00			1.00		
	18	0.86	0.77, 0.96		0.84	0.75, 0.94	
	24	0.88	0.79, 0.98		0.87	0.77, 0.97	
	31	0.91	0.81, 1.01	0.01	0.87	0.77, 0.97	0.002
Alcohol (g)	0	1.00			1.00		
	>0–15	0.96	0.84, 1.10		1.02	0.89, 1.17	
	>15–30	1.01	0.87, 1.17		1.10	0.95, 1.27	
	>30–60	0.93	0.79, 1.10		1.01	0.86, 1.19	
	>60	0.96	0.76, 1.21	0.59	1.08	0.85, 1.36	0.48

* Data on all nutrients except alcohol were energy-corrected by means of the residual method for the analyses. Each nutrient was analyzed separately in a Cox model.

† Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, and energy intake.

‡ *p* for linear trend by the Wald test.

§ Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, energy intake, systolic blood pressure, serum total cholesterol, high density lipoprotein cholesterol, basic education (elementary vs. higher), leisure time exercise, history of diabetes, α-tocopherol and β-carotene supplementation, and smoking cessation.

¶ Referent.

μg/liter. Serum levels were adjusted first for age, smoking habits, and serum total and HDL cholesterol and second for all other risk factors. In both models, risk for claudication was significantly lower with higher levels of serum α-tocopherol (highest quartile vs. lowest: multivariate RR = 0.88 (95 percent CI: 0.77, 1.00); *p* for linear trend = 0.006) and β-carotene (multivariate RR = 0.77 (95 percent CI: 0.68, 0.86); *p* for linear trend < 0.001) (table 4). α-Tocopherol and β-carotene serum levels, when added to the multivariate model simultaneously, retained their significant inverse association (table 4).

DISCUSSION

By far, the most important risk factor for intermittent claudication is smoking. Risk rises with longer exposure time as well as with increasing number of cigarettes smoked per day—a relation clearly shown in our data, as in other prospective studies (5–9). In addition to atherosclerosis, smoking causes vasoconstriction and enhances circulatory carboxyhemoglobin concentration. The decrease observed in risk for intermittent claudication among men who stopped smoking could be explained by improved peripheral blood flow and oxygen supply. Additionally, smoking is suggested to

TABLE 2. Quartile cutpoints for daily intakes of fats and relative risks for intermittent claudication, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–1993*

Fatty acid group	Quartile cutpoints	Age- and smoking-adjusted relative risk†	95% confidence interval	*p* for trend‡	Multivariate relative risk§	95% confidence interval	*p* for trend
Saturated fatty acids (g)		1.00¶			1.00		
	37	1.02	0.90, 1.14		1.04	0.93, 1.17	
	49	1.08	0.97, 1.22		1.08	0.96, 1.21	
	65	1.11	0.99, 1.25	0.09	1.09	0.97, 1.22	0.13
trans-Monounsaturated fatty acids (g)		1.00			1.00		
	2.1	0.96	0.86, 1.08		0.95	0.85, 1.07	
	3.0	0.95	0.85, 1.07		0.95	0.85, 1.06	
	4.4	0.98	0.87, 1.09	0.49	0.98	0.87, 1.10	0.45
cis-Monounsaturated fatty acids (g)		1.00			1.00		
	25	1.09	0.98, 1.22		1.08	0.97, 1.21	
	31	1.03	0.91, 1.15		1.04	0.93, 1.17	
	39	1.05	0.94, 1.18	0.32	1.05	0.93, 1.17	0.32
Polyunsaturated fatty acids (g)		1.00			1.00		
	7	0.96	0.86, 1.07		0.99	0.89, 1.11	
	10	0.86	0.77, 0.97		0.91	0.81, 1.02	
	15	0.89	0.80, 1.00	0.02	0.93	0.83, 1.04	0.15
Polyunsaturated n-3 fatty acids (g)		1.00			1.00		
	1.5	1.01	0.90, 1.12		1.04	0.93, 1.16	
	2.0	0.96	0.86, 1.08		1.02	0.91, 1.14	
	2.7	0.88	0.79, 0.99	0.12	0.94	0.84, 1.06	0.71
Polyunsaturated n-6 fatty acids (g)		1.00			1.00		
	5.4	0.92	0.83, 1.03		0.95	0.85, 1.06	
	7.5	0.85	0.76, 0.96		0.89	0.79, 1.00	
	11.8	0.88	0.79, 0.98	0.005	0.91	0.81, 1.02	0.048
Cholesterol (mg)		1.00			1.00		
	418	1.02	0.91, 1.15		1.02	0.91, 1.14	
	541	1.04	0.93, 1.17		1.02	0.91, 1.15	
	701	1.05	0.93, 1.17	0.40	1.03	0.92, 1.16	0.58

* Data on all nutrients except alcohol were energy-corrected by means of the residual method for the analyses. Each nutrient was analyzed separately in a Cox model.

† Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, and energy intake.

‡ *p* for linear trend by the Wald test.

§ Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, energy intake, systolic blood pressure, serum total cholesterol, high density lipoprotein cholesterol, basic education (elementary vs. higher), leisure time exercise, history of diabetes, α-tocopherol and β-carotene supplementation, and smoking cessation.

¶ Referent.

be associated with lipid peroxidation (29), and in one experimental study, cessation of smoking increased the resistance of low density lipoprotein to oxidation (30).

We observed that the major risk factors for coronary heart disease were significantly associated with risk for intermittent claudication, with the exception of body mass index and diastolic blood pressure. Systolic and diastolic blood pressure are highly correlated with each other; thus, collinearity is a plausible explanation as to why diastolic blood pressure was not associated with claudication. In previous prospective studies, in which diagnosis of intermittent claudication has been

TABLE 3. Quartile cutpoints for daily intakes of antioxidants and relative risks for intermittent claudication, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–1993*

Antioxidant	Quartile cutpoints	Age- and smoking-adjusted relative risk†	95% confidence interval	*p* for trend‡	Multivariate relative risk§	95% confidence interval	*p* for trend
Carotenoids (μg)		1.00¶			1.00		
	2,815	0.88	0.79, 0.98		0.89	0.79, 0.99	
	3,951	0.84	0.75, 0.94		0.87	0.78, 0.98	
	5,562	0.77	0.69, 0.86	<0.001	0.82	0.73, 0.92	<0.001
β-Carotene (μg)		1.00			1.00		
	1,099	0.95	0.85, 1.06		0.96	0.86, 1.07	
	1,727	0.88	0.78, 0.98		0.90	0.81, 1.01	
	2,717	0.83	0.74, 0.93	0.002	0.87	0.78, 0.98	0.02
α-Carotene (μg)		1.00			1.00		
	36	1.00	0.89, 1.12		1.01	0.90, 1.13	
	74	0.93	0.83, 1.04		0.95	0.84, 1.06	
	138	0.88	0.79, 0.99	0.06	0.92	0.82, 1.03	0.21
Lycopene (μg)		1.00			1.00		
	294	0.89	0.80, 1.00		0.91	0.82, 1.02	
	600	0.84	0.75, 0.94		0.87	0.78, 0.97	
	1,041	0.75	0.66, 0.84	<0.001	0.82	0.73, 0.93	<0.001
Lutein + zeaxanchin (μg)		1.00			1.00		
	1,085	0.88	0.79, 0.98		0.89	0.80, 0.99	
	1,383	0.83	0.74, 0.92		0.85	0.76, 0.95	
	1,729	0.78	0.70, 0.87	<0.001	0.81	0.73, 0.91	<0.001
Vitamin E# (mg)		1.00			1.00		
	8.2	0.95	0.85, 1.06		0.98	0.87, 1.09	
	10.8	0.84	0.75, 0.95		0.89	0.79, 1.00	
	14.6	0.88	0.78, 0.98	0.005	0.91	0.81, 1.02	0.06
α-Tocopherol (mg)		1.00			1.00		
	7.1	0.92	0.83, 1.03		0.95	0.85, 1.06	
	9.2	0.88	0.78, 0.98		0.93	0.83, 1.04	
	12.5	0.86	0.77, 0.97	0.006	0.90	0.80, 1.01	0.08
γ-Tocopherol (mg)		1.00			1.00		
	3.1	0.90	0.80, 1.00		0.92	0.83, 1.03	
	5.8	0.83	0.74, 0.93		0.89	0.79, 0.99	
	11.1	0.86	0.77, 0.96	<0.001	0.89	0.79, 1.00	0.02
Vitamin C (mg)		1.00			1.00		
	71	0.85	0.76, 0.95		0.86	0.77, 0.97	
	98	0.87	0.78, 0.97		0.89	0.80, 1.00	
	132	0.82	0.73, 0.92	<0.001	0.86	0.77, 0.97	0.004
Selenium (μg)		1.00			1.00		
	70	1.10	0.98, 1.23		1.09	0.97, 1.22	
	86	1.00	0.89, 1.13		0.99	0.88, 1.11	
	106	1.11	0.99, 1.24	0.15	1.08	0.97, 1.21	0.31

* Data on all nutrients were energy-corrected by means of the residual method for the analyses. Each nutrient was analyzed separately in a Cox model.

† Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, and energy intake.

‡ *p* for linear trend by the Wald test.

§ Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, energy intake, systolic blood pressure, serum total cholesterol, high density lipoprotein cholesterol, basic education (elementary vs. higher), leisure time exercise, history of diabetes, α-tocopherol and β-carotene supplementation, and smoking cessation.

Intake of vitamin E was calculated from intakes of tocopherols and tocotrienols, as follows: α-tocopherol + (0.4 × β-tocopherol) + (0.1 × γ-tocopherol) + (0.01 × δ-tocopherol) + (0.3 × α-tocotrienol) + (0.05 × β-tocotrienol) + (0.01 × γ-tocotrienol).

¶ Referent.

TABLE 4. Relative risks for intermittent claudication by quartiles of serum α-tocopherol and β-carotene levels, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–1993*

	Quartile range	Age-, smoking-, and cholesterol-adjusted relative risk†	95% confidence interval	*p* for trend‡	Multivariate relative risk§	95% confidence interval	*p* for trend	Multivariate relative risk adjusted simultaneously for serum α-tocopherol and β-carotene levels	95% confidence interval	*p* for trend
Serum α-tocopherol (mg/liter)	≤9.75	1.00			1.00			1.00		
	9.76–11.50	0.80	0.71, 0.90		0.83	0.74, 0.93		0.84	0.75, 0.95	
	11.51–13.60	0.80	0.70, 0.90		0.85	0.75, 0.96		0.87	0.77, 0.98	
	≥13.61	0.82	0.72, 0.94	<0.001	0.88	0.77, 1.00	0.006	0.91	0.80, 1.03	0.03
Serum β-carotene (μg/liter)	≤109	1.00			1.00			1.00		
	110–170	0.84	0.75, 0.94		0.91	0.81, 1.01		0.92	0.82, 1.02	
	171–261	0.84	0.75, 0.94		0.94	0.85, 1.05		0.96	0.86, 1.07	
	≥262	0.66	0.59, 0.74	<0.001	0.77	0.68, 0.86	<0.001	0.78	0.69, 0.88	0.002

* To convert values for α-tocopherol to μmol/liter, multiply by 2.322. To convert values for β-carotene to μmol/liter, multiply by 0.001863.
† Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, serum total cholesterol, and high density lipoprotein cholesterol.
‡ *p* for linear trend by the Wald test.
§ Adjusted for baseline age, years of smoking, number of cigarettes smoked per day, serum total cholesterol, high density lipoprotein cholesterol, basic education (elementary vs. higher), leisure time exercise, history of diabetes, α-tocopherol and β-carotene supplementation, and smoking cessation.

based on symptoms similar to those of our study, diabetes or glucose intolerance (5–7, 9), high systolic blood pressure (5–7), and elevated serum total cholesterol level (5, 9) were independent risk factors. HDL cholesterol either was not assessed in these studies (5, 7) or showed no effect after multivariate analysis (6, 9). The association between body mass index and risk for claudication has been inconsistent (5, 9). Higher education was associated with lower risk for claudication in one study (9) but not in another (7).

We found higher intakes of total energy, carbohydrates, and fiber to be protective against claudication. Total energy intake has been inversely associated with risk for ischemic heart disease in some cohort studies (31, 32). A higher level of physical activity is one explanation for this relation, but in our analyses, adjustment for leisure time physical activity did not change the relation. However, the possibility of exercise's being an important mediator cannot be ruled out, as only leisure time exercise was evaluated. A protective effect of high fiber or carbohydrate intake has been reported in a study of peripheral arterial occlusive disease (19) and in some cohort studies of ischemic heart disease (31–35). In our data, men who were in the highest quartiles of fiber and carbohydrate intake also had the highest intake of antioxidants. Thus, the inverse association between carbohydrate and fiber intake and claudication could reflect a high intake of antioxidants and their possible protective effect. One could expect to find a positive association between fat intake and risk for claudication; in our data, however, only n-6 polyunsaturated fatty acids showed a significant association. This finding fits well with results from cohort studies of ischemic heart disease: In different populations, different fatty acids are associated, and the associations are quite weak (11–13, 36). Moderate consumption of alcohol has been protectively associated with peripheral arterial occlusive disease in two studies (19, 37), but we observed no relation between alcohol intake and risk for claudication.

We observed a protective effect of intakes of vitamin C and carotenoids on risk for claudication. In a previous study, dietary β-carotene showed no association (19), whereas in another study a higher intake of vitamin C was associated with lower risk for peripheral arterial disease (20). Of the various carotenoids analyzed in our study, lutein + zeaxanthin and lycopene were most strongly inversely associated with risk for claudication. No previous studies connecting these carotenoids and peripheral atherosclerosis exist, but adipose tissue lycopene level was inversely associated with risk for myocardial infarction in a multicenter case-control study (38). γ-Tocopherol, the second most common dietary tocopherol among our subjects, showed an independent risk reduction effect on claudication, whereas vitamin E and α-tocopherol intake did not. γ-Tocopherol is reported to have an ability to reduce nitrogen dioxide to nitric oxide superior to that of α-tocopherol. However, the possible impact of this mechanism on endothelial function is an open question (39).

Serum α-tocopherol and β-carotene levels were inversely associated with risk for intermittent claudication. To our knowledge, there have been no earlier studies concerning the association between serum antioxidant levels and claudication, but studies on coronary heart disease do exist. In a cross-cultural study (40), low concentrations of α-tocopherol were

associated with increased risk for ischemic heart disease mortality, although no association was reported in three nested case-control studies (41–43). Low serum concentrations of carotenoids have been more consistently associated with higher risk for coronary heart disease in prospective studies (44–46). Our data suggest that α-tocopherol and β-carotene are protective. The difference between our dietary and serum results pertaining to α-tocopherol could be due to measurement errors in dietary assessment leading to attenuation of the dietary association.

In comparison with previous work, a clear advantage of our study was its large size and prospective design. We observed several significant associations between diet and risk for claudication, but compared with the classical risk factors, the associations of different nutrients are only moderate. One must also bear in mind that defining claudication by means of a questionnaire administered once per year will induce some degree of misclassification, and that a certain level of measurement error cannot be avoided in dietary assessments. These shortcomings may have attenuated the true effect of various factors on risk for claudication.

Our material involves a discrepancy between cohort and trial results. We previously reported that long term supplementation with 50 mg of α-tocopherol or 20 mg of β-carotene per day had no primary preventive effect on intermittent claudication among the same men who were subjects of this cohort study (21). Several explanations for these conflicting data exist. The antioxidant hypothesis might hold with physiologic concentrations of antioxidants but not with pharmacologic ones. Thus, supplementation with doses severalfold higher than dietary intake would not be beneficial after all, at least not in a well nourished population. Second, the duration of supplementation may have been too short or supplementation may have occurred at too late an age, whereas dietary intake reflects a lifelong effect. Third, high intakes of specific antioxidants are markers of high consumption of vegetables and fruits. These foods contain many additional compounds, both known and unknown, that may be responsible for the beneficial association observed in epidemiologic studies. Finally, these nutritional factors may reflect mainly lifestyle differences among people who also consume high amounts of vegetables and fruits and those who do not.

In conclusion, we found that the most commonly reported risk factors for coronary heart disease are also risk factors for intermittent claudication. Cessation of smoking is an effective way to reduce risk for intermittent claudication. Furthermore, our data indicate that high intakes of carbohydrates, fiber, n-6 polyunsaturated fatty acids, and antioxidants are protective against intermittent claudication. Carotenoids, especially lycopene, lutein, and zeaxanthin, show the strongest risk reduction. However, their applicability in the prevention of claudication must be confirmed in controlled trials.

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